REMARKS

Claims 22-45 are pending in this application. Claims 1-21 have been previously canceled without prejudice or disclaimer. Applicants have reserved the right to pursue the canceled subject matter in later, to be filed applications. Claim 22 has been amended to recite "wherein said fusion protein has GLP-1 activity." Support for the amendment can be found throughout the specification, for example, in Table 1 on page 49, last row, in Example 116, beginning on page 587, and in Figure 14. Also, the Office noted on page 3 of the Office Action that "claim 45 to the method of treatment of diabetes does not include administration of the composition of claim 44." Therefore, Applicants have amended claim 45, which is directed to the method of treatment of diabetes, to include the administration of the composition of claim 44. Support for the amendment can be found throughout the specification, for example, on page 12, paragraph 45; in Table 1 on page 49; in Table 2 on pages 126 and 130-131, 133-137, and 144; page 218, paragraph 283; and pages 587-589.

Applicants acknowledge, with appreciation, the withdrawal of all prior rejections. The Office has issued one new ground of rejection under 35 U.S.C. § 103(a) against claims 22-45, as being unpatentable over Bequart, *et al.* (EP 0 413 622) in view of Fleer, *et al.* (U.S. Patent No. 5,876,969), Yamamoto, *et al.* (U.S. Patent No. 5,506,120) and Bridon, *et al.* (U.S. Patent No. 6,514,500).

The Office alleges on page 5 of the Office Action that Becquart, *et al.* teach fusion proteins of albumin with therapeutic proteins and that fusing two proteins increases the serum half-life of the therapeutic protein. The Office further alleges that Becquart, *et al.* teach bivalent hybrid protein complexes of the structure CD4-HSA-CD4.

The Office also alleges on pages 5-6 of the Office Action that Fleer, *et al.* teach fusion polypeptides between therapeutic proteins and albumin exhibiting enhanced shelf life and serum half-life. However, the Office acknowledges that both Becquart, *et al.* and Fleer, *et al.* do not teach GLP-1 as the therapeutic protein, nor do they teach arrangement of the multiple copies of the therapeutic protein in a tandem arrangement.

The Office further alleges on page 6 of the Office Action that "Yamamoto et al. teach recombinant production of desired peptides . . . by expressing them as fusions of a proteinaceous carrier [cite omitted] and tandem repeats of desired protein" but acknowledges that "each repeat [is] preceded by a dipeptide linker." The Office further acknowledges that Yamamoto, *et al.* "do not teach GLP-1 as the desired peptide [and that] [t]hey also do not teach albumin as the carrier (although they do teach albumin as a desired peptide [cite omitted])."

Finally, the Office alleges on page 6 of the Office Action that "Bridon et al. teach albumin conjugated through its free thiol to an insulinotropic peptide (ITP) derivatized with a maleimide moiety [and that] GLP-1 and its derivatives are named as an ITP. . . ." The Office admits that Bridon, *et al.* "do not teach fusion of GLP-1 with albumin, nor, of course, in tandem arrangement."

Nonetheless, the Office argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make fusion proteins between albumin and various therapeutic proteins with the expectation of achieving a therapeutic protein having increased serum half-life as taught by Becquart, *et al.* and Fleer, *et al.* The Office further argues that it would have been obvious to place the multiple copies of therapeutic protein taught by Becquart, *et al.* and Fleer, *et al.* in

tandem arrangement as taught by Yamamoto, *et al.* with the expectation of improving the efficiency of expression and that it would have been further obvious to select GLP-1 as the therapeutic peptide in view of the teachings of Bridon, *et al.*

Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP § 706.02(j). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990); MPEP § 2143.01. Moreover, MPEP § 2143.01 instructs that some objective reason to combine the teachings of references is required when the combination of references teach all aspects of the claimed invention. In fact, none of the references cited by the Office, alone or in combination, teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides as required by the instant claims. There is no objective reason to combine the teachings of the references. The references, in fact, teach away from the claimed invention. Therefore, for the reasons set forth in more detail below, the claimed invention is not obvious over the teachings of these references. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

As the Office admits, neither Becquart, *et al.* or Fleer, *et al.* teach GLP-1 as a therapeutic protein, nor do they teach a tandem arrangement of a therapeutic protein. The Office alleges that Yamamoto, *et al.* teach tandem repeats of a "desired" protein,

although they do not teach GLP-1 as the desired peptide. Applicants respectfully submit that not only do Yamamoto, *et al.* fail to teach or suggest GLP-1 as a desired peptide or an albumin fusion protein comprising GLP-1, but Yamamoto, *et al.* also fail to teach or suggest a fusion protein comprising two or more tandemly oriented polypeptides as a therapeutic molecule.

Yamamoto, *et al.* teach tandem repeats of a desired protein merely as an intermediate step in a method for producing single units of the desired protein from the tandem repeats "so that the production and productivity [of the desired protein] can be increased" (col. 8, lines 21-27). To achieve large scale production of single units of the desired protein, Yamamoto, *et al.* teach that "it is necessary to connect the desired peptides via an appropriate spacer and later completely eliminate the spacer from the fusion proteins" (col. 8, lines 35-38). Specifically, Yamamoto, *et al.* teach that:

> mature peptides can be obtained efficiently in large quantities by producing a tandem-type fusion protein with the dipeptide B represented by X_1-X_2 inserted between each two units of the desired peptide and then treating said fusion protein with a combination of a dipeptide-specific protease, paired basic amino acid residues-specific aminopeptidase and a basic amino acid-specific carboxy-peptidase.

Col. 8, line 62 – col. 9, line 2.

As a result, the protease and peptidases cleave between the tandem repeats so that the products produced according to the teachings of Yamamoto, *et al.* are unfused, single units of the desired protein. Thus, Becquart, *et al.*, Fleer, *et al.,* and Yamamoto, *et al. either alone or* in combination provide no motivation to one skilled in the art to prepare or use a fusion protein comprising two or more tandemly oriented polypeptides for therapeutic purposes.

Furthermore, Bridon, *et al.* fail to make up for the deficiencies of Becquart, *et al.*, Fleer, *et al.*, and Yamamoto, *et al.* First, as the Office admits, Bridon, *et al.* teach *chemical conjugates* of insulinotropic peptides, not albumin fusion proteins as required by the instant claims. For example, Bridon, *et al.* teach that the "present invention is directed to modified insulinotropic peptides (ITPs)" (col. 1, lines 43-42) and defines a "modified insulinotropic peptide" as "a peptide that has been modified by attaching a reactive group, and is capable of forming a peptidase stabilized peptide through conjugation to blood components" (col. 4, lines 20-23). "Reactive groups" is defined as "*chemical groups* capable of forming a covalent bond . . . [and] include maleimido groups" (emphasis added, col. 2, lines 55-67).

Second, not only do Bridon, *et al.* fail to teach or suggest an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides, as the Office admits, but Bridon, *et al.*, in fact, teach away from tandemly oriented insulinotropic peptides, including GLP-1. For example, Bridon, *et al.* teach that the advantage of "ITP-maleimide-albumin conjugates is the reproducibility associated with the *1:1 loading of peptide to albumin* specifically at Cys^{34}" (emphasis added, col. 10, lines 46-48) because albumin has only one "free thiol group[, which] . . . is located at amino acid residue 34 (Cys^{34})" (col. 10, lines 24-26). In fact, Bridon, *et al.* teach that "*studies have shown that a 1:1 ratio of therapeutic agent to albumin is preferred*" (emphasis added, col. 10, line 64 – col. 11, line 1). In support of this, Bridon, *et al.* further refer to an article in which the authors report that:

> a 1:1 ratio of the anti-cancer methotrexate to albumin conjugated via glutaraldehyde gave the most promising results. These conjugates were taken up by tumor cells, whereas conjugates bearing 5:1 to 20:1 methotrexate

> molecules had altered HPLC profiles and were quickly taken up by the liver in vivo. *It is postulated that at these higher ratios, conformational changes to albumin diminish its effectiveness as a therapeutic carrier.*

Emphasis added, col. 11, lines 1-13.

Therefore, although the Office cites Bridon, *et al.* as a representative teaching of GLP-1 derivatives because Becquart, *et al.,* Fleer, *et al,* or Yamamoto, *et al.* all fail to teach or suggest an albumin fusion protein comprising GLP-1, Bridon, *et al. teach away from a conjugate comprising more than a 1:1 ratio of ITP (which includes GLP-1) to albumin for use as a therapeutic agent.* As a result, one skilled in the art would not be motivated by any of the cited references, either alone or in combination, to produce or use an albumin fusion protein comprising two or more tandemly oriented GLP-1 polypeptides as required by the instant claims.

In view of the foregoing remarks, Applicants submit that this claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Therefore, Applicants respectfully request the withdrawal of the rejection and for the timely allowance of the pending claims.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Office, placing claims 22-45 in condition for allowance. Applicants submit that the proposed amendment of claim 45 does not raise new issues or necessitate the undertaking of any additional search of the art by the Office, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Office.

Furthermore, Applicants respectfully point out that the final action by the Office presented some new arguments as to the application of the art against Applicant's invention. It is respectfully submitted that the entering of the Amendment would allow the Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the Amendment would place the application in better form for appeal, should the Office dispute the patentability of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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